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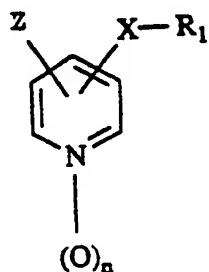
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(54) Heteroaryl amino- and heteroaryloxypyridinamines and related compounds, a process for their preparation and their use as medicaments.

(57) There are described compounds of the formula



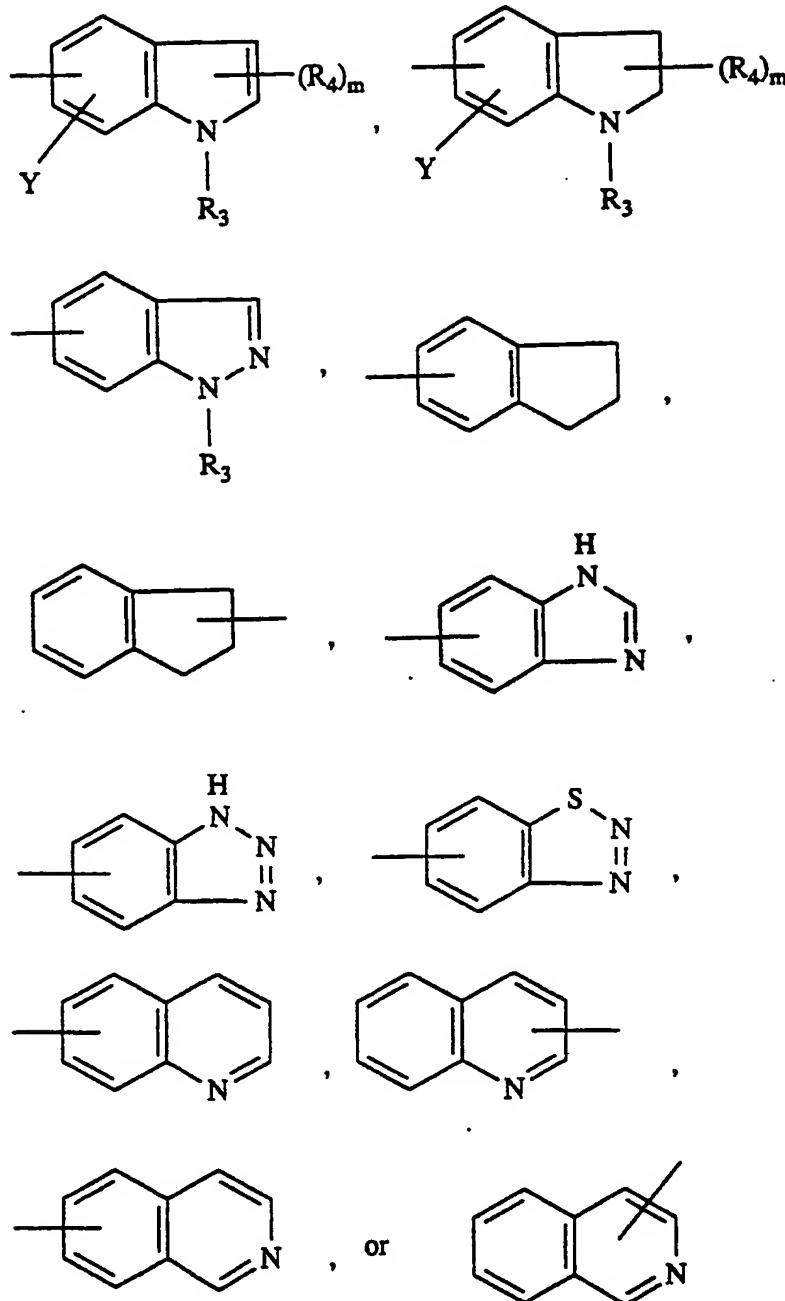
EP 0 405 425 A2

where

n is 0 or 1;

X is O or NR₂, R₂ being hydrogen, loweralkyl or loweralkylcarbonyl; Z is NO₂ or NHR where R is hydrogen, loweralkyl, arylloweralkyl or loweralkylcarbonyl; and

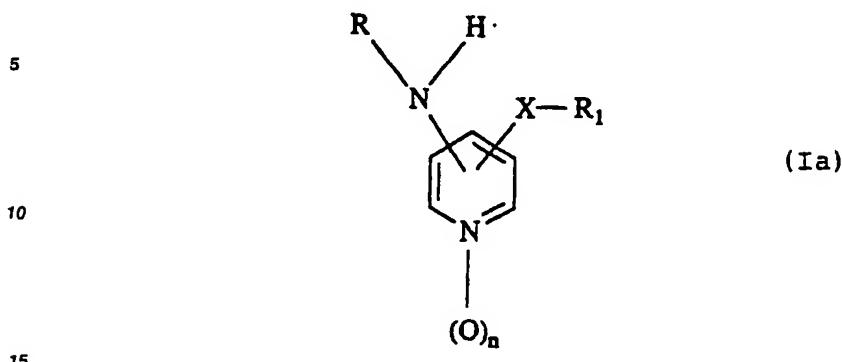
R₁ is



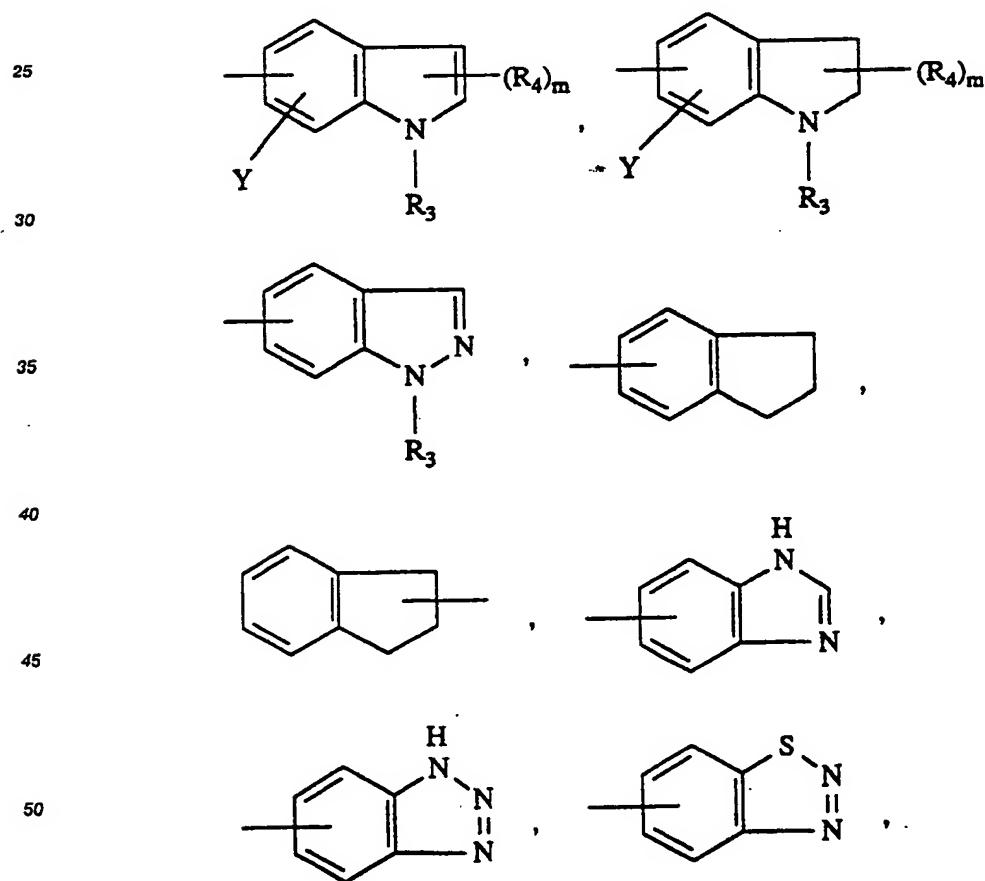
wherein R₃ is hydrogen, loweralkyl or loweralkylcarbonyl; m is 1 or 2; each R₄ is independently hydrogen or loweralkyl; and Y is hydrogen, halogen, loweralkyl, loweralkoxy or trifluoromethyl;
which compounds are useful as topical antiinflammatory agents for the treatment of various dermatoses.

HETEROARYLAMINO- AND HETEROARYLOXPYRIDINAMINES AND RELATED COMPOUNDS, A PROCESS
FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

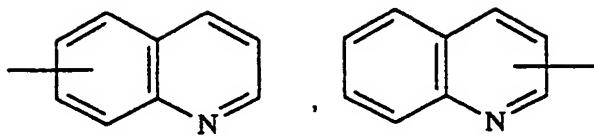
The present invention relates to compounds of Formula Ia



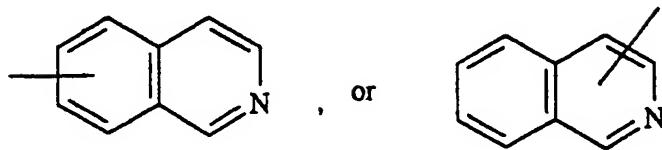
where
n is 0 or 1;
X is O or NR₂, R₂ being hydrogen, loweralkyl or loweralkylcarbonyl;
R is hydrogen, loweralkyl, arylloweralkyl or loweralkylcarbonyl; and
20 R₁ is
R₃ is



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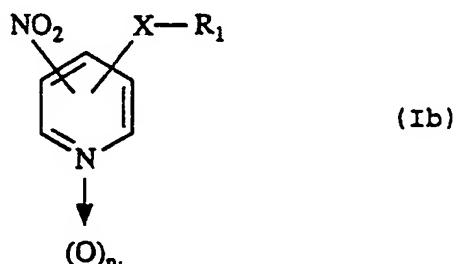


- 15 wherein R₃ is hydrogen, loweralkyl or loweralkylcarbonyl; m is 1 or 2; each R₄ is independently hydrogen or loweralkyl; and Y is hydrogen, halogen, loweralkyl, loweralkoxy or trifluoromethyl;
which compounds are useful as topical antiinflammatory agents for the treatment of various dermatoses including, for example, exogenous dermatitides (e.g. sunburn, photoallergic dermatitis, urticaria, contact dermatitis, allergic dermatitis), endogenous dermatitides (e.g. atopic dermatitis, seborrheic dermatitis, nummular dermatitis), dermatitides of unknown etiology (e.g. generalized exfoliative dermatitis), and other cutaneous disorders with an inflammatory component (e.g psoriasis).

Also included within the scope of this invention are compounds of Formula I b where n, X and R₁ are as defined above, which are useful for the same dermatological applications as mentioned above and also as direct precursors of the compounds of Formula I.

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Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

40 The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said loweralkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

45 The term aryl shall mean a phenyl group optionally mono-substituted with a loweralkyl, loweralkoxy, halogen or trifluoromethyl group.

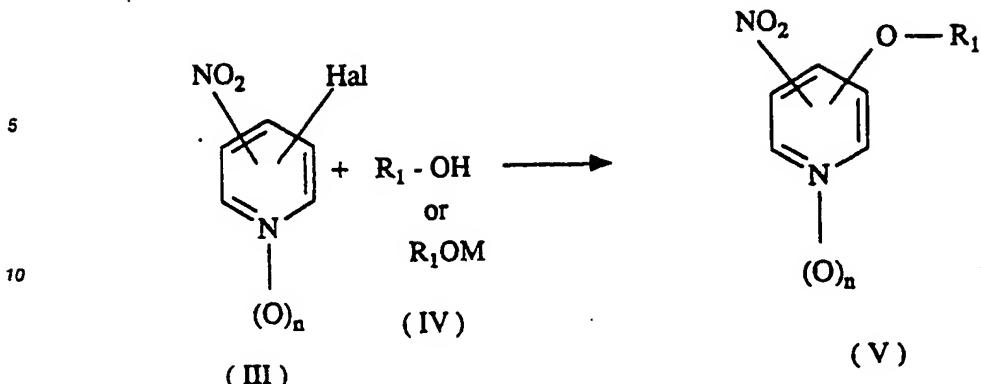
Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo, optical, geometrical and tautomeric isomers where such isomers exist.

The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

50 Throughout the description of the synthetic steps, the notations R, R₁, R₂, R₃, R₄, X, Y, m and n shall have the respective meanings given above unless otherwise stated or indicated, and other notations shall have the respective meanings defined in their first appearances unless otherwise stated or indicated.

55 STEP A:

A compound of Formula III where Hal is F or Cl, preferably F, is allowed to react with a compound of Formula IV where M is Na, K or Li to afford a compound of Formula V.

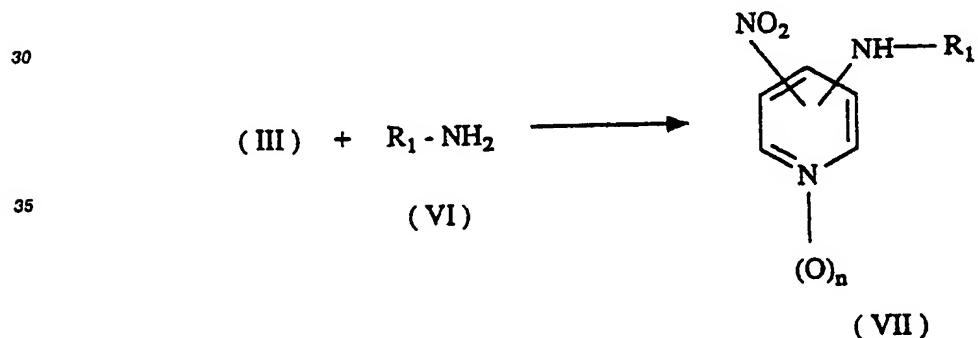


This reaction is typically conducted in a suitable solvent such as ethanol, dimethylformamide, dimethyl-sulfoxide or N-methylpyrrolidone at a temperature of about 0 to 150°C.

3-Fluoro-4-nitropyridine-N-oxide, which belongs to the group of compounds of Formula III, is disclosed in Talik and Talik, Roczniki Chemii, Volume 38, 777 (1964). 4-Chloro-3-nitropyridine, which also belongs to the group of compounds of Formula III, is disclosed in Talik, et al., Roczniki Chemii, Volume 43(5), 923 (1969).

STEP B:

Compound III is allowed to react with a compound of Formula VI to afford a compound of Formula VII.



This reaction is typically conducted in the presence of a suitable solvent such as ethanol, dimethylformamide, dimethylsulfoxide, or N-methylpyrrolidone at a temperature of about 0 to 150 °C.

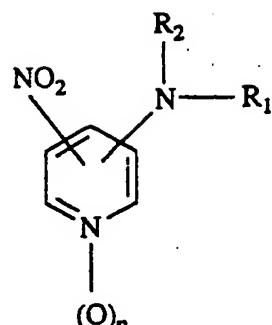
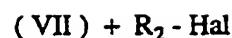
STEP C:

Compound VII is allowed to react with a compound of the formula, $R_2\text{-Hal}$, where R_2 is loweralkyl, arylloweralkyl or loweralkylcarbonyl and Hal is bromine or chlorine in a routine manner known to the art to afford a compound of Formula VIII.

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(VIII)

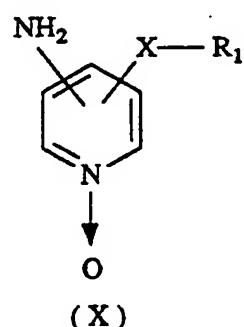
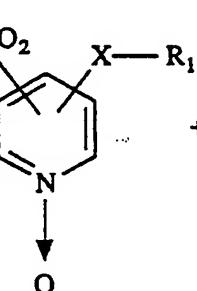
20 STEP D:

A compound of Formula IX which is obtained from STEP A, B or C is selectively hydrogenated to afford a compound of Formula X.

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(IX)

(X)

40 This selective hydrogenation is typically conducted with the aid of a suitable catalyst such as Pd/C, Pt/C or PtO₂ and a suitable medium such as ethanol at a temperature of about 20 to 80 °C.

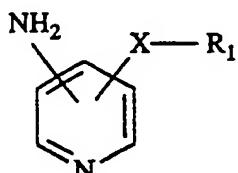
STEP E:

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Compound IX is catalytically hydrogenated in a manner similar to the one described in STEP D above, except that a longer reaction period or higher reaction temperature is preferably employed, to afford a compound of Formula XI.

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(XI)

Instead of using compound IX in the above reaction, one can also use compound X and conduct the hydrogenation in substantially the same manner as described above to obtain compound XI.

5 STEP F:

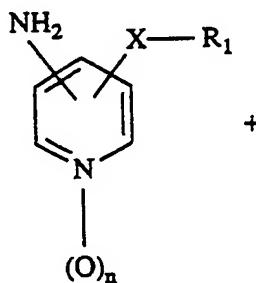
A compound of Formula XII obtained from STEP D, E or G is allowed to react with a compound of the formula, $R_5\text{-Hal}$, where R_5 is loweralkyl, arylloweralkyl or loweralkylcarbonyl and Hal is bromine or chlorine, in a routine manner known to the art to afford a compound of Formula XIII.

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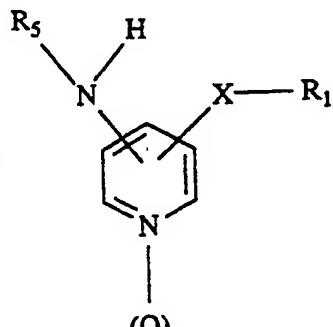
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(XII)

+ $R_5\text{-Hal}$ →

(XIII)

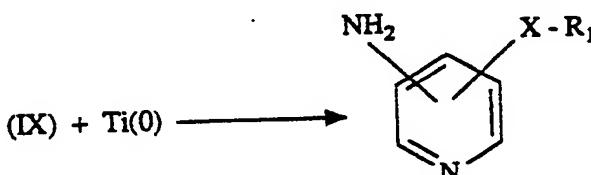
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STEP G:

Compound IX is reduced with a titanium (0) reagent in a routine manner known to the art to afford Compound XI.

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(XI)

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Typically, the titanium (0) reagent is prepared by combining a reducing agent, such as lithium aluminum hydride or magnesium metal, to titanium tetrachloride in an ethereal solvent such as tetrahydrofuran, diethyl ether, diisopropyl ether, or 1,2-dimethoxyethane.

Compounds of Formula I and Formula II according to this invention are useful as topical agents for the treatment of various skin disorders such as those mentioned earlier. The dermatological activities of the compounds of this invention were ascertained with reference to the following methods.

DERMATOLOGICAL TEST METHODS

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Phospholipase A₂-induced Paw Edema (PIPE)

The ability of compounds to prevent naja naja (snake venom) phospholipase A₂-induced paw edema in male Wistar rats (100-125 g) was measured. PLA₂ (3 units/paw) alone or with 0.1 M of the test compound was injected in the subplantar region of the rat left hindpaw. Immediately subsequent to the injection and at two hours post administration the paw was immersed in a mercury bath, and paw displacement was measured on a recorder via a transducer. (Standard: hydrocortisone ED₅₀ = 0.46 M). See Giessler, A.J. et al., *Agents and Actions*, Vol. 10, Trends in Inflammation Research (1981), p. 195.

In Vitro Phospholipase A₂ Assay (PLA₂)

The ability of a compound to modulate PLA₂ activity (cleavage of ¹⁴C-dipalmitoyl phosphatidylcholine at the 2-position to ¹⁴C-palmitic acid) was quantitated in this assay. The reaction mixture contained Tris buffer (25mM) pH 8.0, calcium chloride (2.0 mM), bovine serum albumin (0.5 mg), dipalmitoyl phosphatidylcholine (8x10⁻⁵ M), (¹⁴C-palmitoyl)dipalmitoyl phosphatidylcholine (6x10³ cpm), porcine pancreatic PLA₂ (3.2 units) and the test compound. The reaction was run at 37 °C in a shaking incubator. The reaction was quenched and an internal standard was added in order to determine sample recovery. The samples were loaded onto C₁₈ columns, eluted with ethanol, and the radioactivity was then measured. (Standard: quinacrine IC₅₀ = 3.5x10⁻⁴ M). See Feyen, J.H.M., et al., *Journal of Chromatography* 259 (1983), pp. 338-340.

Arachidonic Acid-Induced Ear Edema (AAEE)

The purpose of this assay was to determine the ability of a topically-applied compound to prevent mouse ear edema induced by topical application of arachidonic acid. Female Swiss Webster mice topically received vehicle or test compound (1.0 mg/ear) on both ears (10 µl on outer and inner ears). After 30 minutes, the right ear of all groups received arachidonic acid (4 mg/ear) and the left ear received vehicle alone. After an additional 1 hour, the mice were sacrificed and an ear punch (4 mm) was taken from each ear. The difference in right and left ear punch weights for each animal was determined to assess activity. (Standard: indomethacin ED₅₀ = 1.5 mg/ear). See Young, J.M. et al., *Invest. Dermatol.*, 80, (1983), pp 48-52.

TPA-Induced Ear Edema (TPAEE)

The purpose of this assay was to determine the ability of a topically-applied compound to prevent ear edema induced by topical application of TPA (phorbol 12-myristate acetate). Female Swiss Webster mice topically received TPA (10 µg/ear) on the right ear and vehicle on the left ear. The test compound (10 µg/ear) was applied to both ears. After five hours, the animals were sacrificed and an ear punch (4 mm) was taken from each ear. The difference in right and left ear punch weights for each animal was determined to assess activity. (Standard: hydrocortisone ED₅₀ = 47 µg/ear). See Young, J.M. et al., *J. Invest. Dermatol.*, 80 (1983), pp. 48-52.

Cultured Human Keratinocyte DNA Synthesis (in vitro DNA)

The effect of a compound on the proliferation of cultured human epidermal keratinocytes was measured. After incubation with a test compound for 24 hours, the cultures were pulse-labelled for three hours with 5 µCi of ³H-thymidine. The cultures were extracted for DNA successively with trichloroacetic acid and ethanol, and thereafter dissolved with NaOH. The radioactive incorporation of ³H-thymidine into DNA was determined. (Standard: indomethacin IC₅₀ = 3.8x10⁻⁵ M).

Epidermal DNA Synthesis (in vivo DNA)

The influence of compounds on the proliferation of skin was assessed by determining inhibition or stimulation of DNA synthesis. HRS/J hairless mice received topical application of a compound or vehicle alone on the dorsal aspect. After 24 hours, ³H-thymidine (25 µCi) was administered by intraperitoneal injection. After an additional hour, animals were sacrificed and the dorsal skin was removed. The epidermal

layer was peeled from the dermis by heat-separation. Unincorporated ^3H -thymidine was removed by washing successively with trichloroacetic acid and ethanol. Samples were centrifuged at 2,000 rpm and supernatants discarded. The epidermal sheets were then extracted with warm trichloroacetic acid and the supernatants analyzed for ^3H -thymidine incorporation by scintillation counting and total DNA by a standard colorimetric assay. (Standard: indomethacin $\text{ED}_{50} = 1.75 \text{ mg/animal}$). See Lowe, N.J., et al., *Arch. Dermatol.*, 117 (1981), pp. 394-8; and Burton, K., *Biochem. J.* 62 (1956), pp. 315-22.

Dermatological activities for some of the compounds of this invention are presented in Table 1.

TABLE 1

	<u>Compound</u>	<u>PIPE*</u> (0.1 M)	<u>PLA₂*</u> (0.01 M)	<u>AAEE</u> (1 mg)	<u>TPAEE</u> (10 μg)	<u>in vivo DNA</u> (2.5 mg)	<u>in vitro DNA</u> (50 μM)
15	N-(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N ⁵ -oxide			-71%			
20	1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N ⁵ -oxide	-41%	-66%		-30%		
25	N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine			-36%			
30	N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N ⁷ -oxide				-40%		
35	N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N ⁵ -oxide				-78%		
40	N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N ⁵ -oxide						
45	N-(4-Nitro-			-83%			

5	3-pyridinyl- 1H-indazol- 6-amine, N ⁶ -oxide					
10	N-(Indan- 5-yl)-4-nitro- 3-pyridinamine- 1-oxide		-44%	-48%		
15	N-(Indan-1-yl)- 4-nitro-3- pyridinamine- 1-oxide			-65%		
20	N-(4-Amino- 3-pyridinyl)- 1H-indol- 5-amine	-67%	-87%	-41%	-85%	-27%
25	N-(4-Amino- 3-pyridinyl)- 1-methyl- 1H-indol-5-amine	-42%	-62%			
30	N-(3-Amino- 4-pyridinyl)- 1H-indol- 5-amine		-82%	-37%		
35	3-[(1H- Indol-5-yl)- oxy]-4- pyridinamine	-62%	-34%	-50%	-42%	-37%
40	1-Acetyl-N- (4-amino-3- pyridinyl)- 2,3-dihydro- 1H-indol-5-amine			-36%		
45	4-[(1H- Indol-5-yl)- oxy]-3- pyridinamine	-52%				
50	N ³ -(Indan- 5-yl)-3,4- pyridinediamine			-49%	-75%	
55	N-(4-Amino- 3-pyridinyl)- 1H-indol- 7-amine, N ⁷ -oxide	-45%			-38%	
	N-(4-Amino- 3-pyridinyl)- 1H-indazol- 6-amine		-57%	-35%		

* difference in edema vs. control

5 Examples of the compound of this invention include:

- N-(4-Amino-3-pyridinyl)-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-1-methyl-1H-indol-5-amine;
 - N-(3-Amino-4-pyridinyl)-1H-indol-5-amine;
 - 3-[(1H-Indol-5-yl)oxy]-4-pyridinamine;
 - 10 1-Acetyl-N-(4-amino-3-pyridinyl)-2,3-dihydro-1H-indol-5-amine;
 - 4-[(1H-Indol-5-yl)oxy]-3-pyridinamine;
 - N³-(Indan-5-yl)-3,4-pyridinediamine;
 - N-(4-Amino-3-pyridinyl)-1H-indazol-5-amine;
 - N-(4-Amino-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide;
 - 15 N-(4-Amino-3-pyridinyl)-1H-indol-7-amine;
 - N-(4-amino-3-pyridinyl)-1H-indazol-6-amine;
 - N-(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide;
 - 1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide;
 - N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine;
 - 20 N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide;
 - 1-Acetyl-2,3-dihydro-N-(4-nitro-3-pyridinyl)-1H-indole-5-amine, N⁵-oxide;
 - N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N⁵-oxide;
 - N-(4-Nitro-3-pyridinyl)-1H-indazol-6-amine, N⁶-oxide;
 - N-(Indan-5-yl)-4-nitro-3-pyridinamine-1-oxide;
 - 25 N-(Indan-1-yl)-4-nitro-3-pyridinamine-1-oxide;
 - 5-[(4-Nitro-3-pyridinyl)oxy]-1H-indole, N⁵-oxide;
 - 5-[(3-Nitro-4-pyridinyl)oxy]-1H-indole;
 - N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine N⁵-oxide;
 - 30 N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine-N⁵-oxide;
 - N-(4-Amino-3-pyridinyl)-N,2,3-trimethyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-iodo-1H-indol-5-amine;
 - 35 N-(4-Amino-3-pyridinyl)-7-chloro-2-ethyl-3-methyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-7-chloro-3-ethyl-2-methyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-trifluoromethyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-methoxy-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-3-isopropyl-2-methyl-1H-indol-5-amine;
 - 40 N-(4-Amino-3-pyridinyl)-7-chloro-2-methyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-7-chloro-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-7-methyl-1H-indol-5-amine;
 - N-(4-Amino-3-pyridinyl)-3-ethyl-1H-indol-5-amine; and
 - N-(4-Amino-3-pyridinyl)-7-bromo-2,3-dimethyl-1H-indol-5-amine.
- 45 The following examples are presented in order to illustrate this invention:

EXAMPLE 1

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N(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide

55 A solution of 3-fluoro-4-nitropyridine-1-oxide ¹ (5 g) and 1H-indol-5-amine (4.2 g) in 100 ml ethanol was

¹Talik and Talik, Roczniki Chemii 38, 777 (1964).

warmed to 80° for one hour and thereafter cooled, and the product was filtered to give 8 g solid, d 244°. Three grams were recrystallized from acetonitrile to give 2.6 g solid, d 244-245°.

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<u>ANALYSIS:</u>				
Calculated for C ₁₃ H ₁₀ N ₄ O ₃ :	57.77%C	3.73%H	20.74%N	
Found:	57.99%C	3.66%H	20.91%N	

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EXAMPLE 2

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1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide

20 A solution of 3-fluoro-4-nitropyridine-1-oxide (6 g) and 1-methyl-1H-indol-5-amine (5.5 g) in 125 ml ethanol was warmed on a steam bath for thirty minutes and thereafter cooled, diluted with ether and filtered to give 10 g solid, d 232-234°. Three grams were recrystallized from ethanol to give 2.2 g needles, d 237-238°.

25

<u>ANALYSIS:</u>				
Calculated for C ₁₄ H ₁₂ N ₄ O ₃ :	59.15%C	4.25%H	19.71%N	
Found:	59.31%C	4.20%H	19.71%N	

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EXAMPLE 3

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N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine

40 To 150 ml of absolute ethanol were added 1H-indol-5-amine (8.06 g), 4-chloro-3-nitropyridine (10.0 g) and triethylamine (8.5 ml), and this mixture was heated to 60°C and stirred for 2 hours. The mixture was cooled, the ethanol evaporated, and the residue taken up in a water/ethyl acetate mixture. This was treated with Na₂CO₃ (aq) to adjust the pH to 10. The organic layer was collected, the aqueous layer extracted again with ethyl acetate, and the organics were combined, washed with water and dried (sat. NaCl, anh. MgSO₄).

45 After filtration, the solvent was evaporated to yield a solid (14.2 g) which was eluted with 5% ethyl acetate/DCM on a silica gel column via flash method. The desired fractions were concentrated to yield a solid (6.1 g). Of this material, 2.0 g was recrystallized from absolute ethanol to yield a solid, 1.2 g, m.p. 204-206°C.

50

<u>ANALYSIS:</u>				
Calculated for C ₁₃ H ₁₀ N ₄ O ₂ :	61.41%C	3.96%H	22.04%N	
Found:	61.41%C	3.96%H	22.00%N	

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EXAMPLE 4

N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide

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To 200 ml ethanol were added 3-fluoro-4-nitropyridine-1-oxide (6.0 g) and 1H-indol-7-amine (5.5 g). After stirring at 85°C for four hours, the mixture was cooled, and the precipitate was collected, washed with methanol, and dried at 60°C overnight to give 9.9 g of solid, m.p. 250°C.

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ANALYSIS:			
Calculated for C ₁₃ H ₁₀ N ₄ O ₃ :	57.78%C	3.73%H	20.73%N
Found:	57.37%C	3.54%H	20.40%N

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EXAMPLE 5

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1-Acetyl-2,3-dihydro-N-(4-Nitro-3-pyridinyl)-1H-indole-5-amine, N⁵-oxide

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A solution of 3-fluoro-4-nitropyridine-1-oxide (4.5 g) and 1-acetyl-2,3-dihydro-1H-indol-5-amine (5 g) in 100 ml ethanol was stirred for two hours at reflux, and thereafter cooled and filtered to give 8.5 g crystals, d₂₃₉₋₂₄₀. Four grams were recrystallized from acetonitrile/ether to give 3 g crystals, d 255-256.

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ANALYSIS:			
Calculated for C ₁₅ H ₁₄ N ₄ O ₄ :	57.32%C	4.49%H	17.83%N
Found:	57.26%C	4.49%H	17.69%N

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EXAMPLE 6

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N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N⁵-oxide

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A mixture of 3-fluoro-4-nitropyridine-1-oxide (6 g) and 1H-indazol-5-amine (5.2 g) in 150 ml of ethanol was refluxed for two hours, and thereafter was cooled, diluted with ether and filtered to give 10 g solid. A 3.5 g portion was recrystallized from ethanol to give 3.0 g solid, d 250.

50

ANALYSIS:			
Calculated for C ₁₂ H ₉ N ₅ O ₃ :	53.13%C	3.34%H	25.83%N
Found:	52.84%C	3.34%H	25.36%N

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EXAMPLE 7

N-(4-Nitro-3-pyridinyl)-1H-indazol-6-amine, N⁶-oxide

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To 100 ml of ethanol were added 3-fluoro-4-nitropyridine-1-oxide (6.0 g) and 1H-indazol-6-amine (5.5 g) and this mixture was heated to 70 °C and stirred for four hours. The mixture was filtered to yield a solid (9.5 g) which was recrystallized from methanol to yield a solid, 6.0 g, m.p. 247-248 °C (decomposed).

10

<u>ANALYSIS:</u>			
Calculated for C ₁₂ H ₉ N ₅ O ₃ :	53.14%C	3.34%H	25.82%N
Found:	52.96%C	3.17%H	25.72%N

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EXAMPLE 8

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N-(Indan-5-yl)-4-nitro-3-pyridinamine-1-oxide

25

A solution of 3-fluoro-4-nitropyridine-1-oxide (12 g) and indan-5-amine (10 g) in 200 ml ethanol was stirred at reflux for two hours, and thereafter cooled, diluted with ether and filtered to give 19 g solid, m.p. 195 °. Four grams were recrystallized from ethanol to give 2.6 g crystals, m.p. 194-195 °.

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<u>ANALYSIS:</u>			
Calculated for C ₁₄ H ₁₃ N ₃ O ₃ :	61.98%C	4.83%H	15.49%N
Found:	62.01%C	4.89%H	15.42%N

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EXAMPLE 9

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N-(Indan-1-yl)-4-nitro-3-pyridinamine-1-oxide

45

A solution of 3-fluoro-4-nitropyridine-1-oxide (5.6 g) and indan-1-amine (6 g) in 100 ml ethanol was stirred at reflux for one hour and thereafter cooled and concentrated to 12 g of solid. This solid was purified by flash chromatography (silica, 10% ethyl acetate in dichloromethane) to give 9.2 g solid, m.p. 137-138 °. An analytical sample was obtained by recrystallizing 2.7 g from ethanol to give 2.5 g crystals, m.p. 141-142 °.

50

<u>ANALYSIS:</u>			
Calculated for C ₁₄ H ₁₃ N ₃ O ₃ :	61.98%C	4.83%H	15.49%N
Found:	62.11%C	4.89%H	15.59%N

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EXAMPLE 10

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5-[(4-Nitro-3-pyridinyl)oxy]-1H-Indole, N⁵-oxide

A solution of 5-hydroxyindole (4.8 g) in 20 ml dimethylformamide was slowly added to an ice cooled suspension of sodium hydride (0.9 g) in 5 ml dimethylformamide. After the anion formation, a solution of 3-fluoro-4-nitropyridine-1-oxide (5.7 g) in 20 ml dimethylformamide was added. After one hour the reaction mixture was stirred with ice water, extracted with chloroform and filtered. The organic extract was washed with water and saturated sodium chloride solution, dried (anhy. MgSO₄), filtered and concentrated to 3.5 g oil. This oil was purified by flash chromatography (silica, 20% ethyl acetate in dichloromethane) to give 2.2 g solid, d 208-210°. This was combined with 2 g product obtained from another condensation and recrystallized from ethanol to give 3 g, d 216-218°.

20

<u>ANALYSIS:</u>				
Calculated for C ₁₃ H ₉ N ₃ O ₄ :	57.57%C	3.34%H	15.49%N	
Found:	57.41%C	3.36%H	15.39%N	

25

EXAMPLE 11

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5-[(3-Nitro-4-pyridinyl)oxy]-1H-Indole

35

To a solution of 5-hydroxyindole (7.45 g) in 100 ml of DMF was added K₂CO₃ (10.4 g). This mixture was stirred for 10 minutes at room temperature and then a solution of 4-chloro-3-nitropyridine (11.89 g) in 50 ml DMF was added dropwise. The reaction was allowed to proceed for 24 hours at room temperature. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl solution and dried over MgSO₄. After filtration, the solvent was evaporated to yield an oil (15.4 g). This material was eluted with 5% ethyl acetate/DCM on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 1.35 g, m.p. 182-184° C.

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EXAMPLE 12

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N-(4-Amino-3-pyridinyl)-1H-indol-5-amine

50

A mixture of N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide (7.8 g) in 500 ml ethanol containing platinum oxide (1.25 g) was hydrogenated at 50 psi for six hours and thereafter filtered and concentrated. The product was purified by flash chromatography (silica, 20% methanol in dichloromethane) to give 6 g solid, m.p. 83-90°. Three grams were distilled twice via Kugelrohr (240-250° @ 0.01 mm Hg) to give 2.4 g solid, 138-140°.

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ANALYSIS:

Calculated for C ₁₃ H ₁₂ N ₄ :	69.62%C 69.21%C	5.39%H 5.47%H	24.99%N 24.80%N
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EXAMPLE 13

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N-(4-Amino-3-pyridinyl)-1-methyl-1H-indol-5-amine

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A suspension of 1-methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N⁵-oxide (6.8 g) in 250 ml ethanol containing 0.4 g platinum oxide was hydrogenated at 50 psi for twenty hours and thereafter filtered through Celite and concentrated to 3.5 g oil. This oil was purified by HPLC (silica 20% methanol in ethyl acetate) to give 2.5 g solid, m.p. 167-169°. This solid was recrystallized from acetonitrile/ether to give 1.1 g solid, m.p. 168-169°.

20

ANALYSIS:

Calculated for C ₁₄ H ₁₄ N ₄ :	70.57%C 70.44%C	5.92%H 5.96%H	23.51%N 23.39%N
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EXAMPLE 14

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N-(3-Amino-4-pyridinyl)-1H-indol-5-amine

To a slurry of 10% Pd/C (1.0 g) in 10 ml of methanol was added N-(3-nitro-4-pyridinyl)-1H-indol-5-amine (4.0 g) in 230 ml methanol and this mixture was hydrogenated at 50 psi on a Parr apparatus. When the reaction was complete, the mixture was filtered through Celite and the filtrate concentrated to yield a solid (3.9 g). This material was eluted with 20% methanol/DCM on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.45 g) which was recrystallized from ethanol/water (10:1) to yield a solid, 1.8 g, m.p. 159-161°C.

45

ANALYSIS:

Calculated for C ₁₃ H ₁₂ N ₄ :	69.62%C 69.63%C	5.39%H 5.46%H	24.98%N 25.07%N
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EXAMPLE 15

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3-[(1H-Indol-5-yl)oxy]-4-pyridinamine

A suspension of 5-[(4-nitro-3-pyridinyl)oxy]-1H-indole, N⁵-oxide (10 g) in 250 ml ethanol containing 0.4 g PtO₂ was hydrogenated at 50 psi for 25 hours and thereafter filtered through Celite and concentrated to 9 g oil. This oil was purified by HPLC (silica, 10% methanol in ethyl acetate) to give 3.5 g solid. This solid was recrystallized from acetonitrile to give 2.4 g crystals, m.p. 170-172°.

5

<u>ANALYSIS:</u>				
Calculated for C ₁₃ H ₁₁ N ₃ O:	69.32%C	4.92%H	18.65%N	
Found:	69.28%C	4.80%H	18.57%N	

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EXAMPLE 16

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1-Acetyl-N-(4-amino-3-pyridinyl)-2,3-dihydro-1H-indol-5-amine

20

A suspension of 1-acetyl-2,3-dihydro-N-(4-nitro-3-pyridinyl)-1H-indole-5-amine (13 g) in 250 ml ethanol containing 0.5 g PtO₂ was hydrogenated for two days at 60 psi and thereafter filtered through Celite and concentrated to 9 g solid. This solid was purified by HPLC (silica, 20% methanol in ethyl acetate) to give 4 g solid. This was combined with 1 g product obtained from a previous reduction and again purified by HPLC (silica, 20% methanol in ethyl acetate) to give 5 g solid, m.p. 210-212°. This solid was recrystallized from acetonitrile to give 4 g solid, m.p. 212-214°.

25

<u>ANALYSIS:</u>				
Calculated for C ₁₅ H ₁₅ N ₄ O:	67.15%C	6.01%H	20.88%N	
Found:	66.84%C	5.95%H	20.80%N	

35

EXAMPLE 17

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4-[(1H-Indol-5-yl)oxy]-3-pyridinamine

To a slurry of 10% Pd/C (1.0 g) in 10 ml of ethanol was added 5-[(3-nitro-4-pyridinyl)oxy]-1H-indole (3.7 g) in 240 ml ethanol and this was shaken on a Parr apparatus for 1 hour. The mixture was filtered and the filtrate concentrated to yield an oil (3.1 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to an oil which solidified on standing to yield 2.6 g, m.p. 155-157° C.

50

<u>ANALYSIS:</u>				
Calculated for C ₁₃ H ₁₁ N ₃ O:	69.32%C	4.92%H	18.65%N	
Found:	69.13%C	4.94%H	18.46%N	

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EXAMPLE 18

N³-(Indan-5-yl)-3,4-pyridinediamine

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A solution of N-(indan-5-yl)-4-nitro-3-pyridinamine-1-oxide (10 g) in 250 ml ethanol containing 0.4 g PtO₂ was hydrogenated at 60 psi for 24 hours and thereafter filtered through Celite and concentrated to 10 g oil. This oil was purified by flash chromatography (silica, 5% methanol in ethyl acetate to give 8.3 g thick oil. This oil was crystallized in diethyl ether to give 5.5 g solid, m.p. 109-110°.

10

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ANALYSIS:

Calculated for C ₁₄ H ₁₅ N ₃ :	74.64%C	6.71%H	18.65%N
Found:	74.81%C	6.72%H	18.71%N

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EXAMPLE 19

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N-(4-Amino-3-pyridinyl)-1H-indazol-5-amine

30

A suspension of N-(4-nitro-3-pyridinyl)-1H-indazol-5-amine, N⁵-oxide (7 g) in 250 ml ethanol containing 0.5 g platinum oxide was hydrogenated at 60 psi for sixty hours and thereafter filtered through Celite and concentrated to 3.3 g solid. This solid was purified by HPLC (silica, 25% methanol in dichloromethane) to give 2.1 g solid. This solid was recrystallized twice from acetonitrile to give 1.5 g crystals, m.p. 198-199°.

35

ANALYSIS:

Calculated for C ₁₂ H ₁₁ N ₅ :	63.98%C	4.92%H	31.10%N
Found:	63.66%C	4.88%H	30.94%N

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EXAMPLE 20

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N-(4-Amino-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide

50

To 250 ml ethanol in a 500 ml Parr hydrogenation bottle were added N-(4-nitro-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide (5.0 g) and 0.4 g PtO₂. After shaking at ambient temperature for twenty-two hours under fifty psi hydrogen, the mixture was filtered and concentrated to a foam, 4.8 g.

This foam was eluted on a silica gel column with 30% methanol/DCM via HPLC. The desired fractions were combined and concentrated to a solid, 2.8 g, m.p. >250° C.

55

ANALYSIS:

Calculated for C ₁₃ H ₁₂ N ₄ O:	64.99%C	5.03%H	23.32%N
Found:	64.57%C	5.12%H	22.78%N

EXAMPLE 21

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N-(4-Amino-3-pyridinyl)-1H-indol-7-amine

10

To 250 ml ethanol in a 500 ml Parr hydrogenation bottle, were added N-(4-amino-3-pyridinyl)-1H-indol-7-amine, N⁷-oxide (2.8 g) and 0.3 g PtO₂. The mixture was shaken at ambient temperature under fifty psi hydrogen for one hour, and thereafter filtered and concentrated to an oil, (2.7 g). This oil was eluted on a silica gel column with 30% methanol/DCM via HPLC. The desired fractions were combined and concentrated to a solid, 2.1 g, m.p. 68-70 °C.

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ANALYSIS:

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Calculated for C ₁₃ H ₁₂ N ₄ :	69.62%C	5.40%H	24.98%N
Found:	68.98%C	5.48%H	24.79%N

25

EXAMPLE 22

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N-(4-Amino-3-pyridinyl)-1H-Indazol-6-amine

35

To PtO₂ (0.3 g) in 10 ml of ethanol was added N-(4-nitro-3-pyridinyl)-1H-indazol-6-amine, N⁶-oxide (2.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus at 60 psi for 20 hours. The mixture was filtered and concentrated to an oil (2.1 g). This material was eluted with 20% methanol/DCM on a silica gel column via HPLC. The desired fractions were concentrated to a solid (0.7 g), which was recrystallized from acetonitrile to yield a solid 0.5 g, m.p. 214-216 °C.

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ANALYSIS:

Calculated for C ₁₂ H ₁₁ N ₅ :	63.99%C	4.92%H	31.09%N
Found:	64.16%C	4.92%H	31.23%N

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EXAMPLE 23

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N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine ethanolate

A mixture of 4-nitro-3-fluoropyridine N-oxide (5.4 g) and 5-amino-2-methylindole (5.0 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50 °C for 30 minutes and then cooled slowly to 0 °C. The precipitate was collected and air dried to give 9.0 g of N-(4-nitro-3-pyridinyl)-2-methyl-1H-indol-5-amine N⁵-oxide as a powder. This powder was taken up in 135 mL of isopropanol and hydrogenated at 50 °C over 3% platinum on carbon at 50 psi in the presence of lithium hydroxide (0.26 g). Filtration and concentration

left 8.0 g of a solid which was recrystallized from 32 mL of methanol giving 4.9 g of crystals. This material was then azeotroped repeatedly with absolute ethanol and dried at 85 °C to give 2.4 g of crystals, mp = 96-98 °C.

5

ANALYSIS:

Calculated for C ₁₆ H ₂₀ N ₄ O:	67.58%C	7.09%H	19.70%N
Found:	67.50%C	7.05%H	19.88%N

10

EXAMPLE 24

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N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine N⁵-oxide hemihydrate

20

A mixture of 4-nitro-3-fluoropyridine N-oxide (5.4 g) and 5-amino-2-methylindole (5.0 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50 °C for 30 minutes and then cooled slowly to 0 °C. The precipitate was collected and air dried to give 8.2 g of N-(4-nitro-3-pyridinyl)-2-methyl-1H-indol-5-amine N⁵-oxide as a powder. This powder was taken up in 255 mL of absolute ethanol and hydrogenated at room temperature over 3% platinum on carbon at 50 psi. Filtration and concentration left 6.4 g of a solid which was purified by HPLC (7:3 dichloromethane/methanol) to give 3.0 g of a powder which was recrystallized from methanol/ether to give 1.8 g of crystals, m.p. 178-180 (with gas evolution).

25

30

ANALYSIS:

Calculated for C ₁₄ H ₁₄ N ₄ O·0.5H ₂ O:	63.86%C	5.74%H	21.24%N
Found:	63.70%C	5.85%H	20.84%N

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EXAMPLE 25

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N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine ethanolate

A mixture of 4-nitro-3-fluoropyridine N-oxide (4.2 g) and 5-amino-2,3-dimethylindole (4.2 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50 °C for 30 minutes and then cooled slowly to 0 °C. The precipitate was collected and air dried to give 7.3 g of N-(4-nitro-3-pyridinyl)-2,3-dimethyl-1 H-indol-5-amine N⁵-oxide as a powder. This powder was taken up in 225 mL of isopropanol and hydrogenated at 50 °C over 3% platinum on carbon at 50 psi in the presence of lithium hydroxide (0.21 g). Filtration and concentration left 4.7 g of a solid which was recrystallized twice from methanol giving 2.4 g of crystals. This material was then azeotroped repeatedly with absolute ethanol and dried at 85 °C to give 1.4 g of crystals, mp = 112-115 °C.

55

ANALYSIS:

Calculated for C ₁₇ H ₂₂ N ₄ O:	68.43%C	7.43%H	18.78%N
Found:	68.31%C	7.50%H	18.61%N

EXAMPLE 26

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N-(4-Amino-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine

A mixture of 4-nitro-3-fluoropyridine N-oxide (1.2 g) and 5-amino-7-chloro-2,3-dimethylindole (1.4 g) in thoroughly degassed absolute ethanol was stirred at 50 °C for 30 minutes and thereafter cooled slowly to 10 °C. The precipitate was collected and air-dried to give 2.37 g of N-(4-nitro-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine N⁵-oxide as a powder.

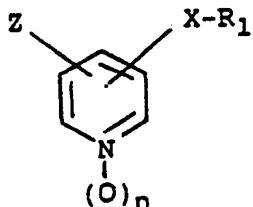
This powder was added in portions to a slurry of titanium powder, prepared from 2.28 g of titanium tetrachloride and 0.45 g of lithium aluminum hydride, in tetrahydrofuran at 0 °C. The reaction mixture was warmed to room temperature and stirred for four hours. The reaction mixture was quenched with dilute ammonium hydroxide and extracted into chloroform. Evaporation of the solvent left a solid which was purified by flash chromatography to give 1.2 g of a powder, m.p. 108-110 °C.

20

Claims

25

1. A compound having the formula I



30

where

n is 0 or 1;

X is or NR₂, R₂ being hydrogen, loweralkyl or loweralkylcarbonyl;35 Z is NO₂ or NHR;

where

R is hydrogen, loweralkyl, arylloweralkyl or loweralkylcarbonyl; and

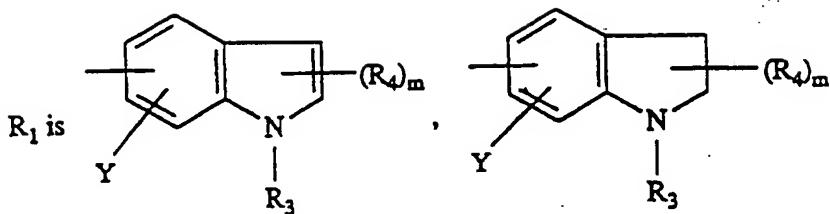
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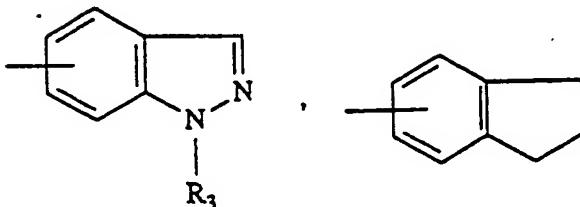
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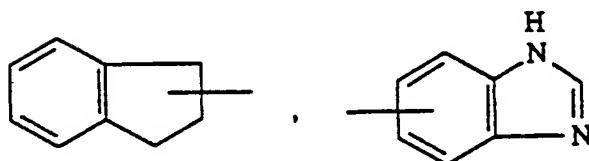


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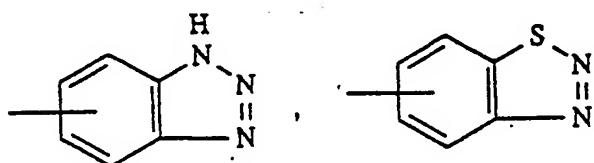


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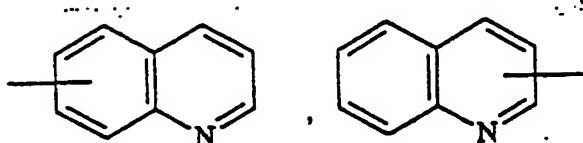


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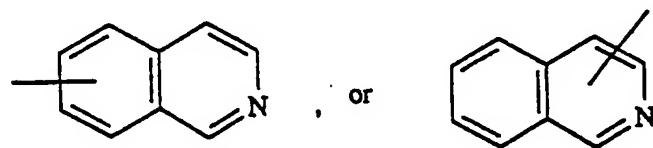


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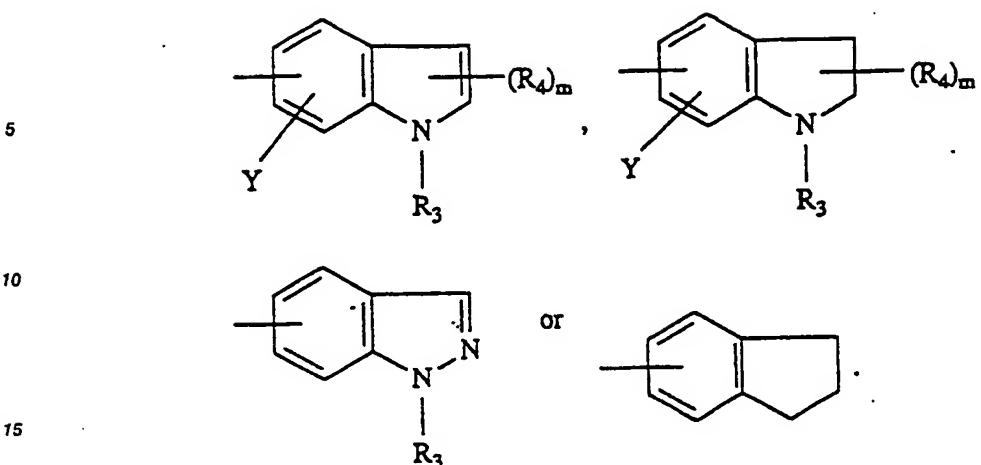


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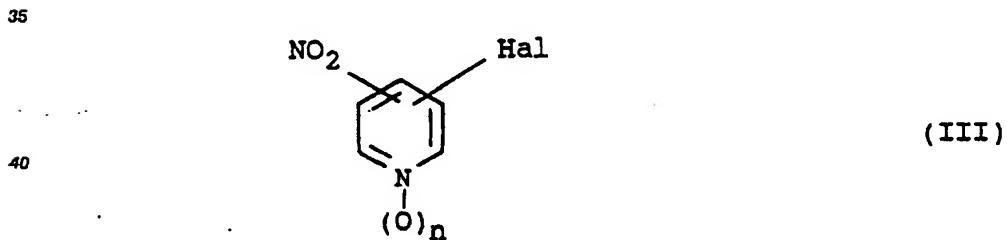
- 45 wherein R₃ is hydrogen, loweralkyl or loweralkylcarbonyl; m is 1 or 2;
 each R₄ is independently hydrogen or loweralkyl; and Y is hydrogen, halogen, loweralkyl or trifluoromethyl;
 or a pharmaceutically acceptable acid salt thereof.
 2. A compound as defined in Claim 1, where X is 0 or NH, and Z is NO₂ or NH₂.
 50 3. A compound as defined in Claim 2, where R₁ is

55



where Y is hydrogen or halogen, and R₃, R₄ and m are as defined in claim 1.

- 20 4. A compound as defined in claim 3, where Y is hydrogen or chlorine, R₃ is hydrogen, methyl or acetyl and R₄ is hydrogen or methyl.
5. A compound as defined in claim 4, where n is 0 and Z is NH₂
6. The compound as defined in claim 5, which is N-(4-amino-3-pyridinyl)-1H-indol-5-amine or a pharmaceutically acceptable acid addition salt thereof.
- 25 7. The compound as defined in claim 5, which is 3-[(1H-indol-5-yl)-oxy]-4-pyridin-amine or a pharmaceutically acceptable acid addition salt thereof.
8. A compound as defined in claim 4 where n is 1 and Z is NO₂.
9. The compound as defined in claim 8, which is N-(4-nitro-3-pyridinyl)-1H-indazol-5-amine, N⁵-oxide.
10. A pharmaceutical composition which comprises as the action ingredient a compound as defined in claim 1 and a suitable carrier therefor.
- 30 11. Use of a compound as defined in claim 1 for the preparation of a medicament being effective against skin disorders.
12. A process for the preparation of a compound as defined in claim 1, which comprises
- a) reacting a compound of the formula III



- 45 45 where Hal is F or Cl and n is as defined above with a compound of the formula R₁-OH or R₁-OM, where R₁ is as defined above and M is Li, Na or K, to afford a compound of the formula I, where R₁ and n are as defined, X is 0 and Z is NO₂, or
- b) reacting a compound of the formula III with R₁-NH₂ where R₁ is as defined above, to afford a compound of the formula I where R₁ and n are as defined, X is NH and Z is NO₂.
- 50 c) optionally reacting a compound of the formula I, where R₁ and n are as defined above, X is NH and Z is NO₂, with a compound of the formula R₂-Hal where Hal is Cl or Br and R₂ is loweralkyl or loweralkylcarbonyl, to afford a compound of the formula I, where R₁ and n are as defined, X is NR₂, R₂ being as defined and Z is NO₂.
- d) optionally selectively hydrogenating a compound of the formula I, where R₁ and X are as defined above, n is 1, and Z is NO₂, to afford a compound of the formula I, where R₁ and X are as defined, n is 1 and Z is NH₂, or
- e) optionally catalytically hydrogenating a compound of the formula I, where R₁ and X are as defined above, n is 1 and Z is NO₂, to afford a compound of the formula I, where X and R₁ are as defined, n is 0

and Z is NH₂.

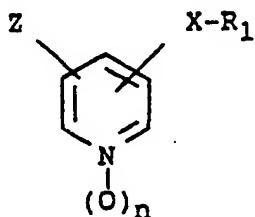
f) optionally reacting a compound of the formula I, where X, R₁ and n are as defined above, and Z is NH₂, with a compound of the formula R-Hal, where R is loweralkyl, arylloweralkyl or loweralkylcarbonyl and Hal is Br or Cl, to afford a compound of the formula I, where X, R₁ and n are as defined and Z is NHR where R is as defined,

5 g) optionally reducing a compound of the formula I, where R₁ and X are as defined above, n is 1 and Z is NO₂, with a titanium (O) reagent to afford a compound of the formula I where R₁ and X are as defined, n is 0 and Z is NH₂.

10 Claims for the following Contracting States: ES,GR

1. A process for the preparation of a compound of the formula I

15



20

where

n is 0 or 1;

25 X is NR₂, R₂ being hydrogen, loweralkyl or loweralkylcarbonyl;

Z is NO₂ or NHR;

where

R is hydrogen, loweralkyl, arylloweralkyl or loweralkylcarbonyl; and

30

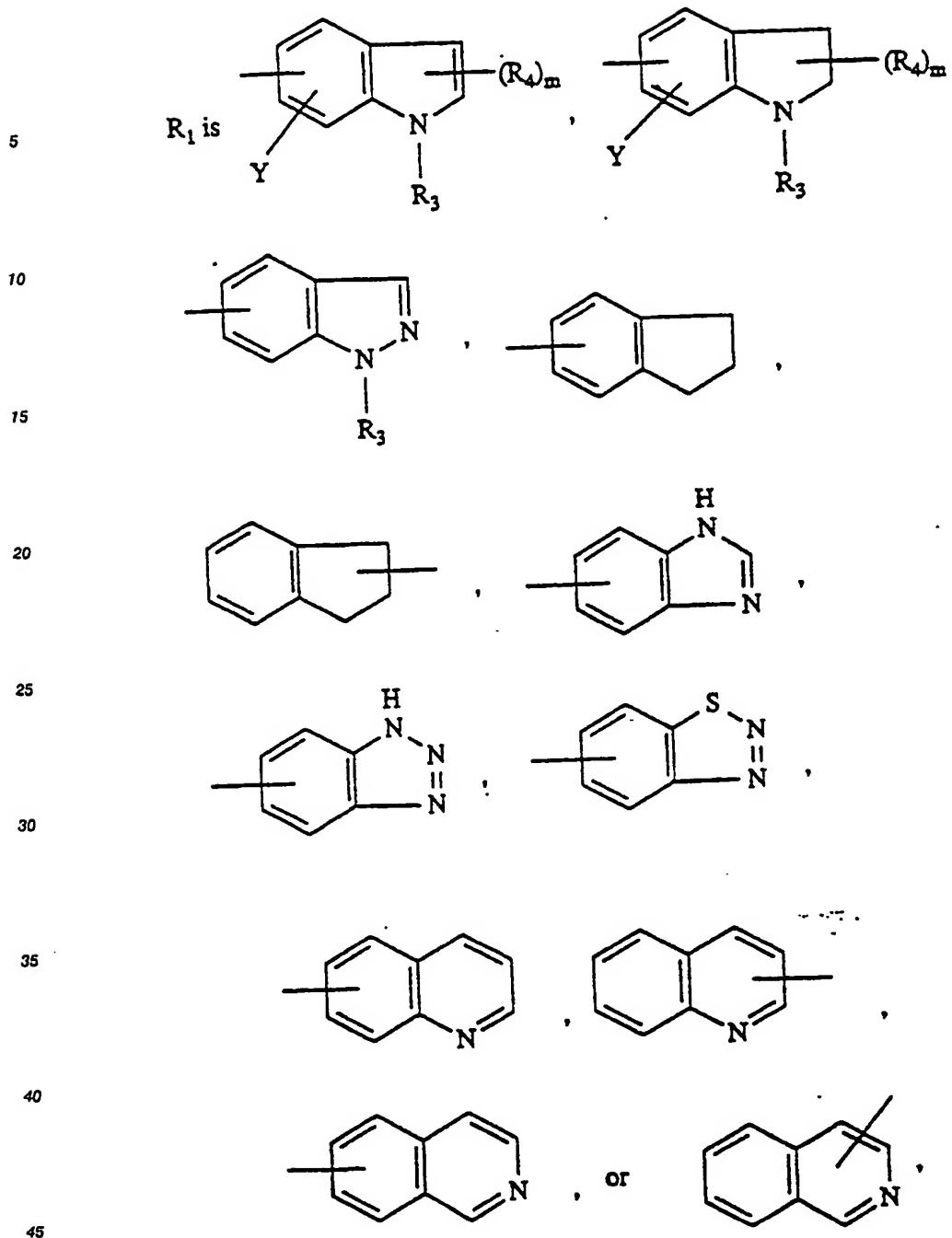
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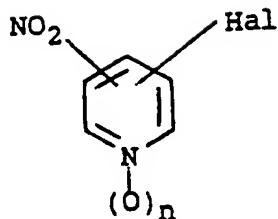
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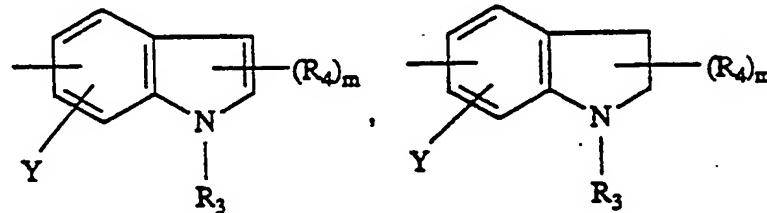


50 wherein R₃ is hydrogen, loweralkyl or loweralkylcarbonyl; m is 1 or 2;
each R₄ is independently hydrogen or loweralkyl; and Y is hydrogen, halogen, loweralkyl, loweralkyl or
trifluoromethyl;
or a pharmaceutically acceptable acid salt thereof which comprises
a) reacting a compound of the formula III



- 10 where Hal is F or Cl and n is as defined above with a compound of the formula R₁-OH or R₁-OM, where R₁ is as defined above and M is Li, Na or K, to afford a compound of the formula I, where R₁ and n are as defined, X is O and Z is NO₂, or
- b) reacting a compound of the formula III with R₁-NH₂ where R₁ is as defined above, to afford a compound of the formula I where R₁ and n are as defined, X is NH and Z is NO₂.
- 15 c) optionally reacting a compound of the formula I, where R₁ and n are as defined above, X is NH and Z is NO₂, with a compound of the formula R₂-Hal where Hal is Cl or Br and R₂ is loweralkyl or loweralkylcarbonyl, to afford a compound of the formula I, where R₁ and n are as defined, X is NR₂, R₂ being as defined and Z is NO₂.
- d) optionally selectively hydrogenating a compound of the formula I, where R₁ and X are as defined above, n is 1, and Z is NO₂, to afford a compound of the formula I, where R₁ and X are as defined, n is 1 and Z is NH₂, or
- e) optionally catalytically hydrogenating a compound of the formula I, where R₁ and X are as defined above, n is 1 and Z is NO₂, to afford a compound of the formula I, where X and R₁ are as defined, n is 0 and Z is NH₂.
- 25 f) optionally reacting a compound of the formula I, where X, R₁ and n are as defined above, and Z is NH₂ with a compound of the formula R-Hal, where R is loweralkyl, arylloweralkyl or loweralkylcarbonyl and Hal is Br or Cl, to afford a compound of the formula I, where X, R₁ and n are as defined and Z is NHR where R is as defined,
- g) optionally reducing a compound of the formula I, where R₁ and X are as defined above, n is 1 and Z is NO₂, with a titanium (O) reagent to afford a compound of the formula I where R₁ and X are as defined, n is 0 and Z is NH₂.
2. A process as defined in claim 1, wherein X is O or NH and Z is NO₂ or NH₂.
3. A process as defined in claim 2, where R₁ is

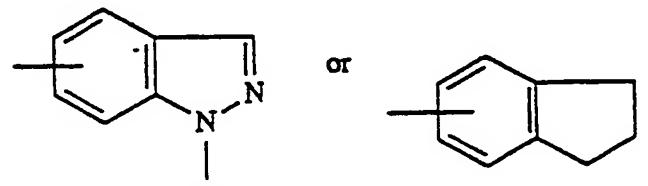
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- where Y is hydrogen or halogen, and R₃, R₄ and are as defined in claim 1.
- 55 4. A process as defined in claim 3, where Y is hydrogen or chlorine, R₃ is hydrogen, methyl or acetyl and R₄ is hydrogen or methyl.
5. A process as defined in claim 4, where n is 0 and Z is NH₂.
6. The process as defined in claim 5, wherein N-(4-amino-3-pyridinyl)-1H-indol-5-amine or a pharmaceuti-

cally acceptable acid addition salt thereof is prepared.

7. The process as defined in claim 5, wherein 3-[(1H-indol-5-yl)-oxy]-4-pyridin-amine or a pharmaceutically acceptable acid addition salt thereof is prepared.

8. A process as defined in claim 4 where n is 1 and Z is NO₂.

5 9. The process as defined in claim 8, wherein N-(4-nitro-3-pyridinyl)-1H-indazol-5-amine, N⁵-oxide is prepared.

10. Use of a compound as defined in claim 1 for the preparation of a medicament being effective against skin disorders.

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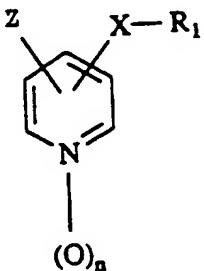
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(54) Heteroarylamino- and heteroaryloxypyridinamines and related compounds, a process for their preparation and their use as medicaments.

(57) There are described compounds of the formula



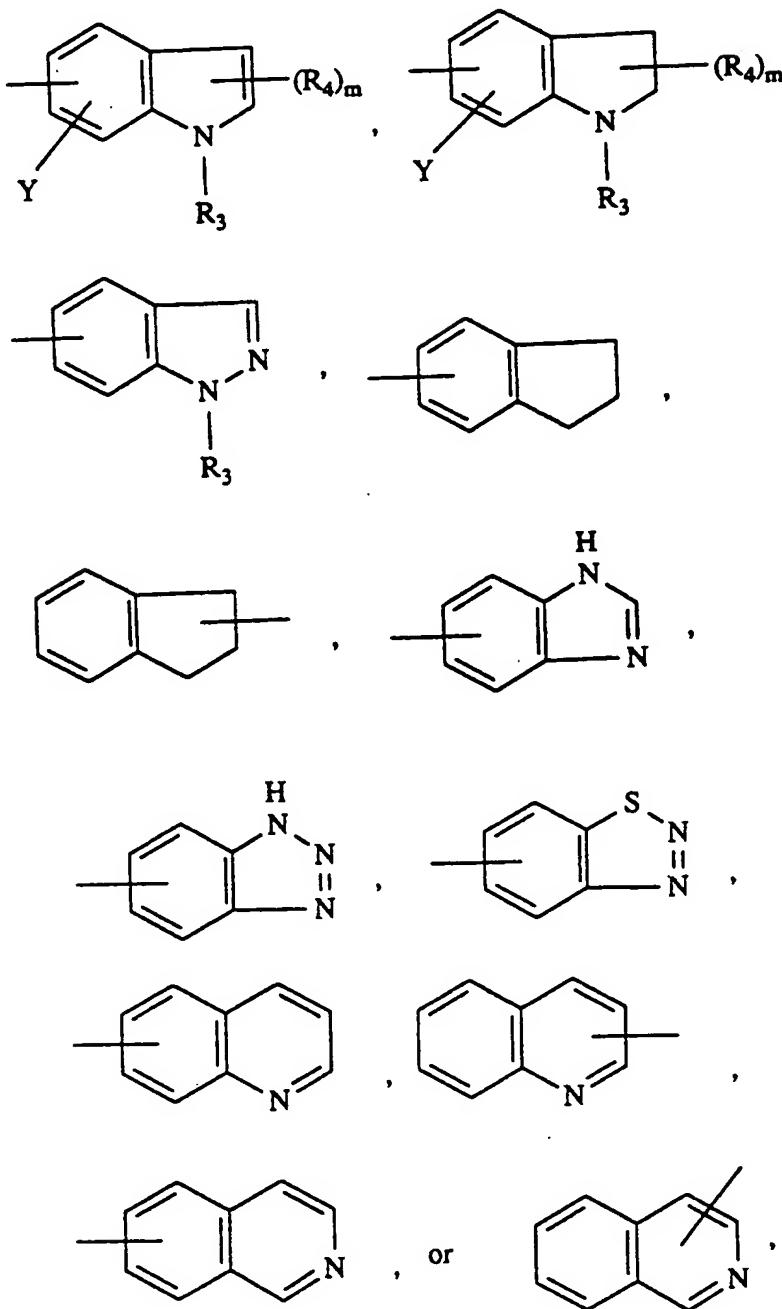
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where

n is 0 or 1;

X is O or NR₂, R₂ being hydrogen, loweralkyl or loweralkylcarbonyl; Z is NO₂ or NHR where R is hydrogen, loweralkyl, aryloweralkyl or loweralkylcarbonyl; and

R₁ is



wherein R₃ is hydrogen, loweralkyl or loweralkylcarbonyl; m is 1 or 2; each R₄ is independently hydrogen or loweralkyl; and Y is hydrogen, halogen, loweralkyl, loweralkoxy or trifluoromethyl;

which compounds are useful as topical antiinflammatory agents for the treatment of various dermatoses.